Brain Environment Interactions: Stress, Posttraumatic Stress Disorder, and the Need for a Postmortem Brain Collection

Elizabeth Osuch, Robert Ursano, He Li, Maree Webster, Chris Hough, Carol Fullerton, and Gregory Leskin

Stress, especially the extreme stress of traumatic events, can alter both neurobiology and behavior. Such extreme environmental situations provide a useful model for understanding environmental influences on human biology and behavior. This paper will review some of the evidence of brain alterations that occur with exposure to environmental stress. This will include recent studies using neuroimaging and will address the need for histological confirmation of imaging study results. We will review the current scientific approaches to understanding brain environment interactions, and then make the case for the collection and study of postmortem brain tissue for the advancement of our understanding of the effects of environment on the brain.

Creating a brain tissue collection specifically for the investigation of the effects of extreme environmental stressors fills a gap in the current research; it will provide another of the important pieces to the puzzle that constitutes the scientific investigation of negative effects of environmental exposures. Such a resource will facilitate new discoveries related to the psychiatric illnesses of acute stress disorder and posttraumatic stress disorder, and can enable scientists to correlate structural and functional imaging findings with tissue abnormalities, which is essential to validate the results of recent imaging studies.

Stress, and in particular the extreme stress of traumatic events, can alter both neurobiology and behavior. Such extreme environmental situations provide useful models for understanding environmental influences on human behavior. Scientific approaches to understanding brain–environment interactions have ranged from animal and human studies, from epidemiology to knock–out rodent studies to experiments on extracted brain cells. Individuals exposed to traumatic events, that is, events which involve extreme disruptions of the environment and the threat of death and injury, experience exceptional physiological and psychological demands. Extreme environmental exposures occur as a result of both natural and human–made traumatic events and disasters, including acts of terrorism, domestic and criminal violence, motor vehicle and industrial accidents, war, domestic rescue missions, and missions of international humanitarian assistance.

Some of the consequences of exposure to these severely traumatic environments may be positive, such as changed values, improved attachment, and enhanced learning and mem-

All authors are affiliated with the Uniformed Services University of the Health Sciences.

Address correspondence to Elizabeth Osuch, MD, Department of Psychiatry, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814. E-mail: eosuch@usuhs.mil.

ory (Holloway and Ursano, 1984; Sledge, Boydstun, and Rabe, 1980; Ursano, 1981). However, other changes may lead to psychopathology (McEwen, 1998a). Negative effects can be short- term as well as long-lasting and may alter function and/or resilience for the duration of the person's life. Cognitive confusion, impaired judgment, altered reaction time, and even temporary paralysis are seen in the acute response to trauma, while chronic effects can lead to Posttraumatic Stress Disorder (PTSD) as well as medical illness, psychosomatic illness, impairments in immune function, alcohol and drug abuse, and depression (Kawamura, Kim, and Asukai, 2001; McEwen, 1998b; North, 2001; North, Spitznagel, and Smith, 2001; Schnurr and Jankowski, 1999; Ursano, 2002; Ursano, Boydstun, and Wheatley, 1981; Yehuda, 2002). These effects are not the result of direct physical damage to the body, but rather are the effect of environmental events on the functioning of the central nervous system and on behavior.

Several psychiatric disorders are thought to arise, at least in part, from exposure to traumatic events: Acute Stress Disorder (ASD), PTSD, Depression, and Adjustment Disorder. Substance use and bipolar disorder are also affected by environmental and developmental events (De Bernardo et al., 2002; Diaz, Simantov, and Rickert, 2002; Dube et al., 2002; Dube et al., 2003; Hyun, Friedman, and Dunner, 2000; Leverich et al., 2003; Leverich et al., 2002; Post et al., 2001; Simpson and Miller, 2002) as well as by genetic predisposition (Itokawa et al., 2003; McGuffin et al., 2003; Ni et al., 2002; Potash et al., 2003). However, PTSD is the only enduring mental illness defined in the *Diagnostic and Statistical Manual* to include an environmental event in its diagnostic criteria (DSM–IV, 1994). ASD is often the prelude to the more long–lasting PTSD and, therefore, may represent the early changes associated with exposure to traumatic stress. These disorders are thus an important focus for examining the impact of the environment on psychiatric disease.

In recent years, advances in our understanding of genetics and gene expression have created increased interest in and knowledge of the interaction of our environment, including developmental factors, with our biology. In the fields of psychiatry and psychology, this topic has long been a focus, usually in the form of the age -old question of the balance of "nature" and "nurture" in the determination of behavior. At the same time that researchers are investigating candidate genes for mental illnesses such as bipolar disorder, autism and schizophrenia, studies are demonstrating that environmental influences across the various stages of an animal or human's life have significant effects on behavior and brain physiology. Recent studies have helped to overcome the dichotomy between genetic and environmental influences by demonstrating that environmental events alter gene expression——whether a gene is turned on or off——thereby changing the physiology of neurons, synapses and hence neuronal networks, leading to alterations in behavior. In other words, we now know that the environment can influence behavior through changes in gene expression.

It is clear that the genetic makeup of an individual can lead to some illnesses with near certainty, such as Huntington's Chorea and early onset Alzheimer's Disease (Nussbaum, McInnes, and Willard, 2001). However, psychiatric conditions generally do not follow simple, single–gene modes of inheritance. Rather, they result from a combination of the complex interplay of "susceptibility genes" and environmental and developmental events (Gilger, 2000; Rutter, 2002). For example, early life experience has been shown to determine anxious behavior, together with the endocrine function of the hypothalamic–pituitary–adrenal (HPA) axis, in adult rodents (Francis et al., 1999; Liu et al., 1997; Zaharia et al., 1996). Early life experience seems to override genetic differences such that "genetically anxiety prone" infant rodents become non–anxious adults if they are reared by high "licking and grooming" mothers (Meaney, 2001). Alternatively, studies of poor socialization, aggressive behavior and serotonin levels in rhesus monkeys demonstrate a combination of the effects of genes and early develop-

mental influences, with both a genetic susceptibility and poor rearing environment combining to result in a poor outcome (Bennett et al., 2002; Suomi, 2003).

With increased understanding of the effects of environment on gene expression and neurobiology, the new focus of scientific and clinical concern is how much of any given behavior or mental illness is inevitable given our genetics at birth, and how much is influenced by the gene–environment interactions. The answer to this question may be essential for the prevention of some mental diseases. Thus, illnesses with a heavier environmental loading may be best prevented by avoiding exposure to certain environmental stimuli or by fostering alternative environmental exposures. (From this perspective, psychotherapy, as well as parent–child interactions, diet and other externally originating influences, may be of import.) Illnesses with a greater genetic loading may benefit from a more biomedical and eventually, perhaps, a gene–therapy approach to treatment, since environmental effects are less influential. If we can understand the relationships among environmental stimuli and genetic effects, we will be better able to propose both environmental and biological therapies.

For ASD and PTSD, where a specific event and reaction to the event are integral to the onset of the condition, understanding the genetic predisposition and vulnerability of the individual *as affected and modified by the environment* is critical to optimally preventing the disorders and treating the patient. Because some people develop impairment after a traumatic event while many do not, we can ask, "Did some factor(s), including genetic composition or early life event pre–date the traumatic event and contribute to the onset of the pathology?" Prospective, longitudinal studies looking at genes and environment can help in answering this question. Such studies are possible in populations that we know will be exposed to extreme stress, such as police officers and soldiers. However, it is often inefficient and expensive to identify a population at risk, study them before they experience a traumatic event, and then study them after the event. A combination of investigational paradigms to look at genetic and environmental factors is most likely to lead to fundamental new knowledge and treatment for those exposed to traumatic events.

Research using postmortem tissue has advanced our knowledge in many areas of medicine. Brain "banks" and other collections of human tissue are well known in the study of dementia, multiple sclerosis, and genetic diseases. However, this tissue has not been available for the study of Posttraumatic Stress Disorder (PTSD), Acute Stress Disorder (ASD) or other brain–environment related neurobiological conditions. In order to advance our present experimental paradigms for studying the interactions of neurobiology, genetics and the environment, consideration needs to be given to developing opportunities for postmortem human brain tissue studies. Postmortem human brain tissue from individuals exposed to environmental stressors, who had a variety of behavioral symptoms, can be compared with healthy exposed and unexposed controls. Such studies will critically contribute to the science and clinical care of individuals exposed to traumatic events. A brain collection for the study of the effects of extreme environmental exposure can enable scientists to investigate tissue, protein and genetic abnormalities in previously symptomatic and asymptomatic human subjects and, thus, confirm and expand the extant research. Postmortem analyses are essential for resolving some of the critical research questions necessary to understanding and preventing the negative effects of environmental influences.

This paper will update the reader on some of the evidence of brain alterations that occur with exposure to environmental stress, including some of the findings of neuroimaging and the need for histological confirmation of imaging study results; it will, review the current scientific approaches to understanding brain environment interactions, and then make the case for the use of postmortem brain tissue for advancing the field of understanding the effects of environment on the brain. A glossary accompanies the text to fa-

cilitate the appreciation of the material by readers who may not be in the field of neuroscience.

EVIDENCE OF BRAIN ALTERATIONS WITH ENVIRONMENTAL STRESS

Although it might be assumed that schizophrenia and affective disorders are more "biologically" based and, thus, more likely to be accompanied by alterations in microscopic brain structure, there is an abundance of evidence that environmental stress can result in the modification of brain chemistry, gene expression and, particularly if occurring during development, even brain structure (Teicher et al., 2003). Similarly, the neurobiological basis of PTSD is an area of intense investigation in biological psychiatry. Brain regions that mediate affective responses, such as the amygdala, are affected by the experience of severely traumatic events, leading to a pathological form of emotional memory (Cahill et al., 1995; Davis, 1994; Davis, Walker, and Lee, 1997; Gallagher and Chiba, 1996; Phelps and Anderson, 1997; Rogan, Staubli, and LeDoux, 1997; Watanabe, et al., 1996). In order to better understand what we know about the effect of the environment on the human organism, the following section delves more deeply into several specific areas of scientific inquiry in both humans and other animals as they relate to the understanding of the interaction of environment and the neurobiology of human behavior. By reviewing this material, some of the progress—and some of the complexity—of this area of research becomes more evident.

Neuroimaging

The field of structural and functional brain imaging is now a central tool for our investigation of the relationship of brain and environment. Brain imaging has flourished in the past 10 years. In addition to the use of structural magnetic resonance imaging (MRI) to obtain images of extraordinary spacial resolution of brain structures, the field of functional neuroimaging has developed. This technology detects markers of brain function. Specifically, with the use of single photon emission computed tomography (SPECT) and positron emission tomography (PET) (with a wide variety of radio–ligands that bind to blood cells or particular biochemical markers), scientists are able to gain information about the activity of brain regions under a variety of circumstances. More recently, the advent of functional magnetic resonance imaging (fMRI) has resulted in neuroimaging with both excellent spacial and temporal resolution, and thus, resulting in much more accurate viewing of brain activity. This technology is now being widely used in psychiatry and neurology research to investigate normal and abnormal brain function never before observable. However, the exact nature of these "indirect" measures of brain structure and function still need to be investigated by tissue examination from human brains.

Using *structural* neuroimaging techniques, there are many studies demonstrating abnormalities in the volume of various brain structures (see Figure 1) in subjects with PTSD. These brain areas include the hippocampus, a region known to be involved in memory (Bremner et al., 1995; Bremner, et al., 1997b; Gurvits, et al., 1996; Schuff et al., 1997; Stein et al., 1997), and other brain regions (De Bellis et al., 1999). Hippocampal volume changes do not seem to be acute effects of severe environmental exposures (Bonne et al., 2001) but rather are present in patients with chronic PTSD and may, in fact, be a predisposing risk factor for PTSD (Gilbertson et al., 2002). It is not clear whether, or in what manner, the volumetric abnormalities are causally related to symptoms, nor is it entirely clear which cell types or cell processes may be responsible for the volumetric differences.

Using *functional* imaging techniques, numerous groups have studied cerebral blood flow in subjects with chronic PTSD using an auditory script or medication challenge to reproduce subjects' symptoms (Bremner et al., 1999a; Bremner et al., 1999b; Liberzon et al.,

1999; Osuch et al., 2001; Rauch et al., 1996; Shin et al., 1997; Shin et al., 1999; Zubieta et al., 1999). In general, studies support activation in the right (Rauch et al., 1996; Shin et al., 1997) or left (Liberzon et al., 1999) amygdala, and in the sensorimotor cortex (Bremner et al., 1999a; Bremner et al., 1999b; Osuch et al., 2001; Rauch et al., 1996). Several fMRI studies suggest abnormally low response of anterior cingulate cortex and thalamus in subjects with PTSD compared with non–PTSD trauma exposed controls (Lanius et al., 2001; Lanius et al., 2003; Shin et al., 2001).

In one study using a radioligand for the benzodiazepine receptor, Bremner et al. (Bremner et al., 2000) demonstrated decreased benzodiazepine receptor binding in the prefrontal cortex of Vietnam veterans with PTSD compared to control subjects. Another fMRI study of PTSD has shown an exaggerated amygdala response to a non–specific negative emotional stimulus (Rauch et al., 2000). The cellular mechanisms whereby cerebral blood flow is altered in specific brain regions with symptom provocation or other challenges in PTSD subjects remain unknown.

Functional imaging studies can involve paradigms designed to activate particular brain area(s) by using specific tasks or stimuli. For example, the use of "fearful faces" has been shown to activate the amygdala, a brain region known to be important for emotion recognition and processing (Whalen et al., 1998). In this paradigm, the subject is placed in an fMRI scanner and shown the images of faces on a display. The faces may be displayed for a long enough time to be recognized and recalled, or they may be "masked" by a face with a neutral expression. The "masked face" is shown for a very short period of time, right before the neutral face is shown, and is "seen" for so short a period of time that the subject does not consciously perceive it and denies seeing anything but the masking face. The masked face depicts a face with an expression of fear.

Interestingly, the fearful subliminal face results in activation of the amygdala, suggesting that even though the person had no awareness of the image, their brain did actually register it. Subjects with PTSD have an increase in activation of the amygdala, compared with healthy controls, with the use of the masked faces paradigm (Rauch et al., 2000). This type of study indicates that there are functional alterations in specific brain structures in subjects with PTSD. These alterations may be related to behavioral consequences such as increased fear responses seen in individuals with PTSD.

Studies of altered cerebral structure and function require histological confirmation with postmortem tissue analysis since all imaging modalities are indirect and involve a number of assumptions. Without the use of tissue analysis as the "gold standard" to verify neuroimaging findings, the functional imaging results in the study of stress related psychopathology remain disconnected from cellular and genetic mechanisms.

Acoustic Startle

The acoustic startle response is a muscular contraction (e.g., eye blink) with heart rate elevation and skin conductance alterations following exposure to sudden, loud sounds. It is seen in all mammals, including humans, and involves a reflex pathway that begins in the auditory system, travels to the brainstem, and ends in motor neurons (in the spinal cord and cranial nerves). Exaggerated acoustic startle response, or "hyperstartle," is one of the common features of PTSD, and is a symptom that patients with the disorder often find disturbing—reporting distress that they jump and become acutely afraid when surprised by a loud sound. The study of the physiology of acoustic startle is important to understanding PTSD, and thus basic brain–environment interactions.

While not under conscious control, startle response is increased if a subject is afraid, and decreased if a subject is relaxed or has taken anxiolytic medication. Numerous studies have demonstrated that the acoustic startle response in rodents is enhanced by stressful stimuli such as intermittent tail shock (Garrick et al., 1997; Garrick et al., 2001), foot shock (Shi and Davis, 2001), and other

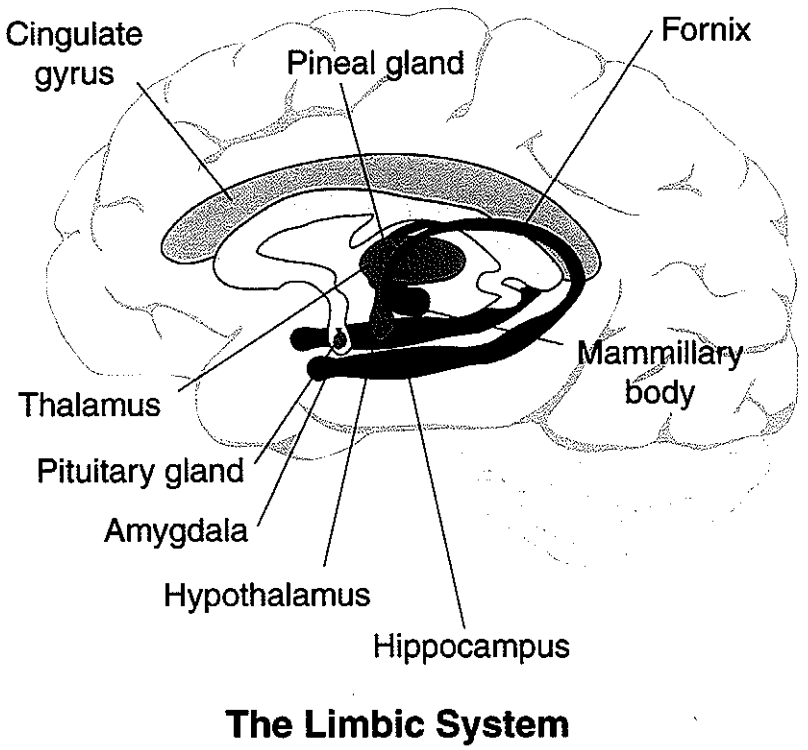

Figure 1.
Depiction of the human brain highlighting some of the various structures that relate to processing of emotion.

stressful conditions, such as bright light (in a nocturnal species)(Walker and Davis, 2002). These studies demonstrate that acoustic startle is affected by environmental conditions, and can thus function as an interesting model for PTSD and the effects of stress on humans.

Abnormalities in acoustic startle, related either to the eye–blink or autonomic response, have been demonstrated in subjects with PTSD and/or traumatic exposures of various kinds (Morgan et al., 1997; Morgan et al., 1996; Orr et al., 1997; Shalev et al., 1997). The effect of environmental or chemical manipulations in altering the startle response in individuals with PTSD has been analogous to the studies in stressed rodents, demonstrating enhanced startle with threat of electric shock (Grillon et al., 1998b), startle exaggeration when placing the subjects in a darkened room (Grillon et al., 1998a), or when giving human subjects yohimbine to facilitate autonomic arousal (Morgan et al., 1995). Recently, Shalev et al., demonstrated that the altered startle responses occur within four weeks after a traumatic event in subjects who developed PTSD (Shalev et al., 2000), suggesting that the abnormality occurs in the aftermath of the traumatic event, not before. This lends credence to the notion that the abnormal startle reaction emerges from the traumatic experience rather than that abnormal startle preexists or predisposes to PTSD.

Animal studies have greatly aided our understanding of the fundamental neurobiology of the startle response. Using animal studies that produce lesions in various brain areas and/or by introducing substances into specific brain structures, Mike Davis and

others (Birnbaum and Davis, 1998; Gewirtz, McNish, and Davis, 1998; Lu, Walker, and Davis, 2001; Meloni and Davis, 1999, 2000a, 2000b, 2000c; Pelton, Lee, and Davis, 1997) have learned about the physiology of acoustic startle. Such studies have helped to delineate the roles of dopamine, serotonin, NMDA, and GABA in acoustic startle modulation. Needless to say, similar studies are not possible in live humans, but alterations in this reflex circuit could be examined in postmortem tissue when it becomes available.

Neurochemistry

The discussion of some the neurochemistry of traumatic exposure and response presented here may be difficult for some readers not familiar with the field. While the details are meaningful, the overarching message is more meaningful: neurochemical brain changes after exposure to traumatic environments have behavioral effects. It is neurochemistry that lies between environmental events and subsequent behavior of the individual. Clarifying the neurochemistry is another compelling reason for postmortem research in this area.

One of the often replicated findings in PTSD patients is an increase in heart rate, blood pressure, and urinary and plasma levels of norepinephrine and epinephrine upon presentation of a "reminder" of the traumatic events (Bremner et al., 1997a; Bremner et al., 1996; Mason et al., 1988; Murburg et al., 1995). Neuronal connections, transmission and synaptic release of neurotransmitters are central to this response (see Figure 2). The increased autonomic responsiveness appears to be mediated by release of catecholamines, which act on target tissues via α and β–adrenergic receptors (Bremner et al., 1996; Southwick et al., 1993; Southwick et al., 1997b). Following multiple inescapable tailshocks, rats exhibit an increase in turnover and release of norepinephrine in cerebral cortex and several subcortical areas, including amygdala, hippocampus, hypothalamus, and locus coeruleus (Bremner et al., 1996; Li et al., 1998; Southwick et al., 1993; Southwick et al., 1997b; Tsuda et al., 1989). In addition, there may also be activation of the serotonergic system (Southwick et al., 1997a).

Increased release of norepinephrine and serotonin in the amygdala is associated with behaviors that are typically seen during states of fear, suggesting that norepinephrine and serotonin may play a role in amygdala circuits mediating fear responses (Servatius, Ottenweller and Natelson, 1995). Norepinephrine and serotonin may, therefore, also participate in the synaptic plasticity phenomena that result in the memory of frightening events in PTSD in humans.

Recently, norepinephrine and the α2 adrenergic receptor agonist UK 14304 have been shown to inhibit excitatory synaptic transmission in the basolateral amygdala and the α2 receptor antagonist yohimbine blocks this effect, suggesting that α2 receptor agonists are able to modulate excitatory synaptic function in the amygdala (Ferry, Magistretti, and Pralong, 1997). Administration of the α2 adrenergic receptor antagonist yohimbine results in flashbacks in 40% and panic attacks in 70% of Vietnam War veterans with combat–related PTSD, suggesting that norepinephrine's action on α2 receptor of the amygdala neurons may contribute to the prevention of traumatic recall (Bremner et al., 1997a; Bremner et al., 1996; Mason et al., 1988; Murburg et al., 1995). Decreased α2 adrenergic receptor expression has been found in patients with PTSD compared to controls, suggesting that increased release of norepinephrine may induce down–regulation of these receptors (Mason et al., 1988; Murburg et al., 1995; Yehuda et al., 1992). Intracellular calcium, guanosine trisphosphate protein (GTP), and calcium channels are also related to activation of these α2 receptors by norepinephrine (Inukai, Wang, and Greer, 1992; Negresku et al., 1989; Schwartz, 1997; Zelis and Moore, 1989).

Emotional memories can also be modulated by adrenal stress hormones, including epinephrine and glucocorticoids (Quirarte, Roozendaal, and McGaugh, 1997; Roozendaal, Quirarte, and McGaugh, 1997).

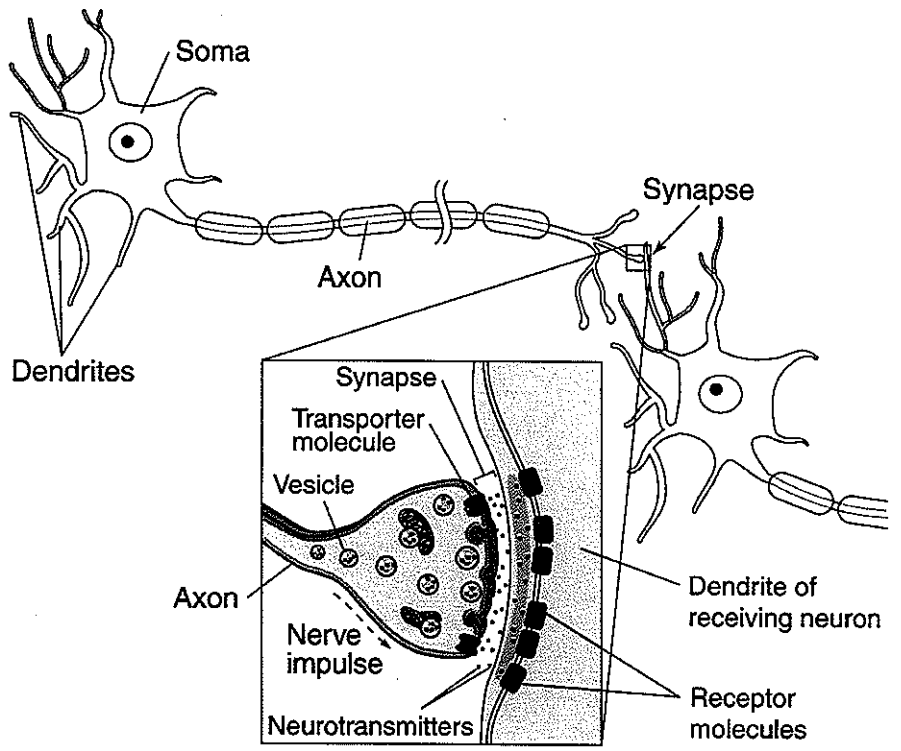

Figure 2.
Structure and function of the neuron emphasizing the transmission and release of neurotransmitters.

Epinephrine enhances emotional memory through activation of β–adrenergic receptors (Introini–Collison et al., 1992). Recently, several studies in humans have also indicated that activation of β–adrenergic receptors can influence long–term declarative memory formation for emotionally arousing events (Cahill et al., 1994; Nielson and Jensen, 1994). This is thought to be part of why memories of emotionally laden events are so much more vivid and long–lasting than memories of neutral events. In the hippocampus propranolol, a β–receptor antagonist, is capable of blocking activity–dependent long–term potentiation induction of both lateral and medial perforant path–evoked field excitatory postsynaptic potentials (Bramham, Bacher–Svendsen, and Sarvey, 1997). In synaptic transmission between basolateral amygada and ventral endopyriform nucleus, activation of β–adrenergic receptors by isoproterenol also causes an increase of intracellular c–AMP, and induces a long–term enhancement of excitatory postsynaptic potentials (Huang, Hsu, and Gean, 1996). These findings can facilitate the development of preventive interventions following exposure to traumatic events.

These examples of the neurobiological alterations sample a large body of research on animals and humans, and point towards effects that may be studied with the use of post-mortem tissue. While the chemical alterations just described may be investigated and understood, in part, by using methods of isotope imaging in the live human, the more fundamental questions of alterations in gene expression

and resultant cellular changes that lead to these biochemical alterations cannot be discovered without the use of human brain tissue.

SCIENTIFIC APPROACHES TO UNDERSTANDING GENES AND THE ENVIRONMENT

Several approaches to understanding the predisposing and sustaining factors of psychiatric illness have developed within the social, behavioral, and neurobiological sciences and are used in our efforts to understand environment–gene interactions resulting in ASD and PTSD. These approaches span many species (Figure 3) from yeast to humans and many levels of observation from the atomic and molecular to the societal (Figure 4). We will discuss the general approach and some of the important findings from four general strategies of investigating psychiatric disorders: epidemiology, clinical trials, animal studies, and pathology.

Epidemiological studies are integral to defining the population(s) at risk and the natural course of illnesses affecting human behavior. Epidemiologic studies of the genetic influences on human behavior use methodologies such as family and twin studies in humans, and genetic analyses comparing healthy control subjects with people suffering from various mental illnesses. *Clinical trials* of medications and/or behavioral interventions are extremely important for developing treatment interventions for disorders. *Animal studies* involve organisms less complex than humans and provide much of the understanding of the essential mechanisms of physiological function and malfunction, and as such are indispensable components of human research. *Pathology research* looks at the tissue of humans and other animals after the death of individuals with mental illness in the former, and intentional alterations of genes and/or environment in the latter. Let us consider these research approaches in turn as they have contributed to our understanding of trauma responses.

Epidemiological studies following natural disasters, combat, and criminal exposure offer information about the behavior of humans after these kinds of events, but are unclear regarding possible genetic/biological factors. Forty–five percent of survivors of the Oklahoma City bombing had a post–disaster psychiatric disorder. Of those, 34.3% had PTSD and 22.5% had major depression (North et al., 1999). Nearly 40% of those with PTSD or depression had no previous history of psychiatric illness. The psychosocial, cognitive, and biologic effects of traumatic events are complex and interrelated (McEwen, 2001; Ursano, 2002; Yehuda, 2002). For most individuals, posttraumatic symptoms are transitory. However, for some, the effects of trauma linger long after its occurrence, awakened by reminders. In its acute form, PTSD may be more like the common cold, experienced at some time by all (Fullerton, Ursano, Norwood, & Holloway, 2003). However, if it persists, it can be debilitating and require substantial treatment. The rates of PTSD after serious traumatic events vary from approximately 12% after molestation in males to 45–65% after rape (Kessler et al., 1995). If one examines a randomly selected traumatic event, nearly 9.2% of people will develop PTSD, and nearly one-third of cases will become chronic (Kessler, 2003).

Clinical trials of various medications and therapies have been helpful in developing treatments of mental illnesses, including PTSD. The work of Foa et al. has demonstrated the usefulness of systematized exposure therapy for women who recently experienced sexual or other assault (Foa et al., 1999; Foa, Hearst–Ikeda, and Perry, 1995; Foa et al., 1991). There have been several well–controlled medication trials using antidepressants (Brady et al., 2000; Connor et al., 1999; Davidson et al., 1990; Davidson et al., 2001; Frank et al., 1988; Marshall et al., 2001; Martenyi et al., 2002; Neylan et al., 2003; Rapaport, Endicott, and Clary, 2002; Tucker et al., 2001; van der Kolk et al., 1994) as well as both preliminary and controlled studies using anticonvulsants to treat PTSD (Berlant and van Kammen, 2002; Brannon, Labbate,

and Huber, 2000; Clark et al., 1999; Fesler, 1991; Hamner, Brodrick, and Labbate, 2001; Hertzberg et al., 1999; Lipper, 1988; Lipper et al., 1986).

There are yet to be found agents which could be given in the immediate aftermath of a traumatic event to prevent the development of PTSD, although the use of beta-blockers is promising (Pitman et al., 2002). Not only do such studies improve clinical practice and, thereby, reduce the human suffering associated with such illnesses, but they also shed light on the pathophysiology of the condition. Clinical trials, however, do not directly address the biological processes of the pathology.

Animal models serve to fill some of the gaps in the study of the pathophysiology of mental illnesses. Animal studies allow investigators to directly measure variables in the brain in ways not possible in humans. However, the use of non-human animals is complicated by the challenges of translating behavior and physiology across species. Some of what constitutes symptoms of mental illness in humans is experienced as perceptions and sensations that are not immediately measurable from outside the patient (such as hallucinations, flashbacks, and dysphoria), and may have no obvious equivalent in rodents or non-human primates. Allowing for these challenges of interpretation, there have been many impressive advances in understanding the way in which gene and environment interact, using a variety of animal species. In some cases, animal models are demonstrating ways in which gene expression is responsible for complex social behaviors not previously understood nor previously thought of as under the purview of genetic explanation. For example, the work by Tom Insel et al., on monogamy in vole species has uncovered the role of vasopressin, oxytocin, and dopamine in determining monogamous versus promiscuous behavior in these mammals (Gingrich et al., 2000; Insel and Hulihan, 1995; Insel et al., 1995; Wang et al., 1997; Wang et al., 1999; Wang et al., 2000). Research in non-human species is important and necessary for advancing human research.

Some of the early work on the role of the nervous system on behavior in response to the environment was conducted by Eric Kandel on the marine invertebrate Aplysia (snail). Using this organism, he showed that repeated stimulation with an inert (neither rewarding nor aversive) stimulus resulted in a decrease in the animal's response to the stimulus. This was a consequence of a decrease in the synaptic effectiveness of the pathways to the motor neurons compared with when first administered (Kandel, 1991). While this may seem like a small discovery, it paved the way to understanding how humans learn to ignore extraneous and unimportant environmental stimuli——a problem for people with several mental illnesses, from attention deficit disorder and schizophrenia to PTSD. More recently, studies in rodents demonstrated a connection between the gene for a substance known as gastrin-releasing peptide (a substance usually thought of in relation to gut activity, but now found in the amygdala——a region of the brain involved with fear), and the extent to which an animal learns to fear a particular stimulus (Shumyatsky et al., 2002). These studies help to delineate the mechanisms by which environmental stimuli interact with and affect the brain at a cellular level, thereby leading to emotionally driven behaviors.

Sometimes it is also possible to use animal models to simulate human conditions or diseases. This allows for the study of the mechanisms of disease, and the use of various interventions to prevent or treat the condition. There are animal models for arthritis, leprosy, and numerous other medical conditions. In the behavioral sciences, it has been challenging to develop animal models for disorders such as schizophrenia, bipolar disorder, and depression. The animal models of learned helplessness (Edwards et al., 1991; Hughes et al., 1984; Seligman, 1975; Telner and Singhal, 1984; Weiss et al., 1985) and social defeat (Lumley et al., 1999) have been helpful for emulating some aspects of depression. Animal models of PTSD and severe stress have included tail shock paradigms in rodents (Servatius et al., 1995), a form of learned helplessness (King, Abend, and Edwards, 2001), and the chronic exposure to

the adrenal hormone corticosterone (Levy, Kadar and Dachir, 2001).

"Knock–out" studies in mice, in which a gene is disabled, allow us to look at the direct effects of a gene by observing what happens to animal physiology and behavior in the complete or near–complete absence of a gene (Alberts et al., 2002). These include studies of catecholamine activity (Shih and Chen, 1999), effects of the dopamine receptor (Elmer, Elston, and Libow, 2002; Ralph et al., 1999), the dopamine transporter (Ralph et al., 2001), and the role of long–term potentiation in learning and memory (Fukunaga and Miyamoto, 2000; Huang and Stevens, 1998).

Pathology research involves the investigation of the tissue of animals and humans to identify alterations that have occurred, either with a certain disease compared with healthy tissue, or after a particular intervention. In animals, pathological analyses are combined with models of disease states. The process involves inducing the model of disease in the animal, then sacrificing it and investigating the tissue with a variety of chemical, genetic, or other agents. In humans, pathology research is conducted on surgical specimens removed from people during clinically necessary operations, or from postmortem autopsy specimens after death. Clinical neuropathology research in humans also involves evaluating people who have had brain surgery, penetrating injuries to the brain, or closed head injuries such as those caused from high impact automobile collisions. Some of the earliest understanding of the function of the hippocampus, for example, came from the study of an individual, referred to by the initials H.M., who had a surgical resection of both temporal lobes, including the hippocampal cortices (Milner, 1966; Milner, Corkin, and Teuber, 1968; Sidman, Satoddard, and Mohr, 1968; Wickelgren, 1968). Of all the scientific approaches, postmortem pathological analysis, involving direct analysis of tissue, is a gold standard for verifying pathology and pathophysiology in biological research.

A NEW AND NECESSARY SCIENTIFIC APPROACH

The Importance of Postmortem Brain Tissue

There are over 55 postmortem brain repositories in the United States today, most of which collect tissue for the study of neurological disorders, including Alzheimer's Disease, Parkinson's Disease, HIV, other dementias, Huntington's Disease, and traumatic brain injury.[1,2,3,4,6] A smaller number of laboratories collect tissue for the investigation of neuropsychiatric disorders such as schizophrenia, bipolar affective disorder, and substance abuse[2,5,6,7,8,9,10,11,12,13,14], and for developmental disorders such as autism. The oldest federally funded postmortem brain tissue collection, the *Human Brain and Spinal Fluid Resource Cen-*

1. *National Neurological Research Specimen Bank*, VA Greater Los Angeles Healthcare System; Los Angeles, CA
2. *Harvard Brain Tissue Resource Center*, Harvard Medical School; Belmont, MA
3. *Stanford University Brain Collection*, Stanford University/VA Palo Alto Healthcare System; Stanford, CA
4. *University of Washington Brain Collection*, Department of Psychiatry and Behavioral Sciences; Seattle, WA
5. *NIMH Brain Collection*, NIH/NIHM/Clinical Brain Disorders Branch; Bethesda, MD
6. Mount Sinai School of Medicine, Department of Psychiatry; New York, NY
7. University of Mississippi, *Laboratory of Quantitative Neuroanatomy*; Jackson, MS
8. *Maryland Psychiatric Research Center*; Baltimore, MD
9. *University of Miami School of Medicine Brain Endowment Bank*; Miami, FL
10. *Stanley Brain Research Laboratory and Brain Collection*; Bethesda, MD
11. *New York Brain Bank*, Columbia University; New York, NY
12. *The Brain Tissue Donation Program*, University of Pittsburgh Medical Center; Pittsburgh, PA
13. *University of California Irvine Brain Repository*; Irvine, CA
14. *University of Colorado Health Sciences Center*; Denver, CO

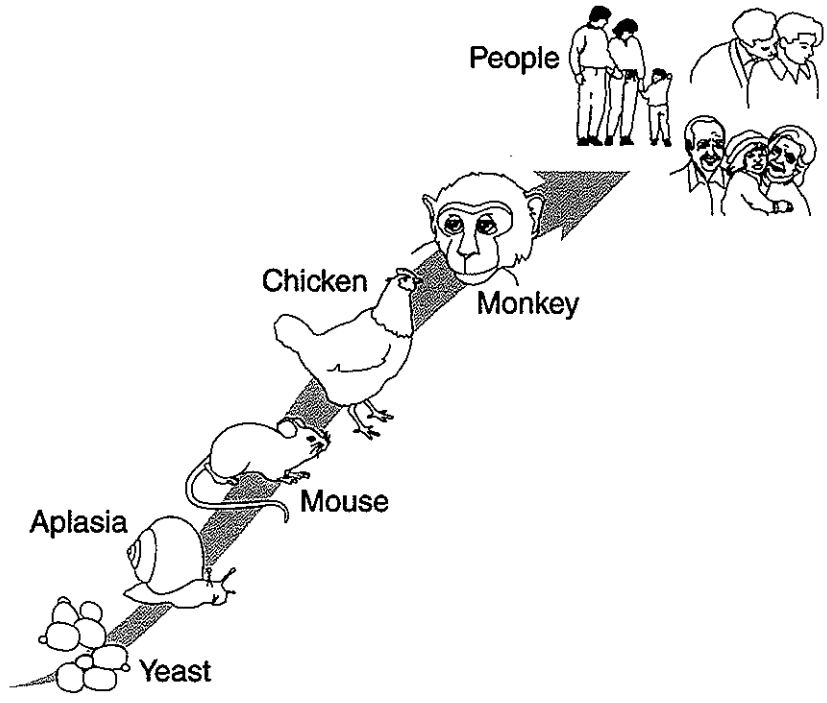

Figure 3.
The continuum of species studied to understand environment-gene interactions and their resulting psychopathology spans from yeast to humans.

ter, was established in 1961 and is housed by the Los Angeles Healthcare System. This organization has collected over 11,000 brains for the study of neurological and psychiatric conditions. The *Stanley Brain Research Laboratory* (Torrey et al., 2000) opened in 1994 and has collected over 500 brains for investigation of schizophrenia, bipolar disorder, and unipolar depression.

Recent research using postmortem brain tissue has resulted in the discovery of key proteins in the development and maintenance of neurons in brain areas important for cognition and judgment (such as Reelin of Cajal–Retzius cells). The revolution in the neurosciences resulting from advancing technology in functional brain imaging and studies of neuronal apoptosis, regeneration, and the effects of stress and excitotoxicity provide important evidence for the biological elements of neuropsychiatric disorders. Such studies have radically changed the way researchers think about mental illness. Studies currently in progress with postmortem brain samples from psychiatric cases include investigation of cytoarchitectonics, neurotransimitters and receptors, neuropeptides, enzyme synthesis, neurotropic factors, synaptic proteins, signal transduction pathways, and markers of inflammation and infection. Numerous abnormalities in cellular architecture, protein expression, and mRNA expression, have been described (Harrison, 1999, 2002). For example, Rajkowska (Rajkowska, 2000) has shown alterations in both neuronal and glial cell morphometry in bipolar disorder and depression.

The laboratory of David Lewis has discovered abnormalities in gene expression within neurons of the prefrontal cortex of

schizophrenia patients using postmortem tissue analyses (Hashimoto et al., 2003). Caberlotto and Hurd (Caberlotto and Hurd, 1999) found a decrease in neuropeptide Y mRNA expression in subjects with bipolar disorder as compared to controls. Individuals with bipolar disorder (Shimon et al., 1997) and schizophrenia (Shimon et al., 1998) show a decrease in second messenger inositol levels in the frontal cortex. Tyrosine kinase receptor mRNA levels are reduced in the frontal cortex of individuals with schizophrenia (Schramm et al., 1998), as is glycogen synthase kinase–3 (Kozlovsky, Belmaker, and Agam, 2000). Jarskog et al. (Jarskog et al., 2000) reported a reduction of the potent inhibitor of apoptosis, Bcl–2, in the brains of subjects with schizophrenia as compared to controls.

While studies such as these, examining the expression of one gene or protein at a time, have yielded large amounts of data and shed some light on possible etiology and targets for therapeutic intervention, they are time–consuming and require relatively large quantities of tissue. The recent introduction of cDNA microarray technology to neuropsychiatric research has enabled the profiling of gene expression patterns of tens of thousands of genes in a single experiment (Schena, 1996; Schena et al., 1998; Schena et al., 1995). Several studies using microarrays have already identified abnormalities in categories of genes that suggest certain systems or biochemical pathways that are significantly affected in neuropsychiatric disorders (Bezchlibnyk et al., 2001; Hakak et al., 2001; Middleton et al., 2002; Mirnics et al., 2000; Vawter et al., 2001; Vawter et al., 2002). However, because gene expression is not necessarily temporally correlated with actual protein expression, we now see proteomic studies emerging that can examine hundreds of proteins in one experiment (Johnston–Wilson et al., 2000; Rohlff, 2000, 2001; Weinberger et al., 2001). Moreover, the technology is evolving so rapidly that array and proteomic studies can now be conducted on single morphologically identified cells dissected from histological sections (Hemby et al., 2002; Ohyama et al., 2002; Simone et al., 2000).

Studies based on these technologies will establish global gene and protein expression profiles of given disorders that will illuminate the complex gene–environment interactions of neuropsychiatric disorders. Ultimately, the identified pathways will aid in our understanding of the pathophysiology of these disorders, and result in advances in diagnosis and treatment. The successful application of these molecular technologies, however, requires the collection of well–characterized postmortem tissue.

The Role of a Postmortem Brain Laboratory for Severe Trauma Events

The overarching goal of establishing a collection of human brain tissue following acute and chronic severe traumatic events is to provide researchers with samples that will lead to the discovery of the pathophysiological basis of negative reactions to traumatic environments. With the use of postmortem human brain tissue, the connections among animal studies, human epidemiological studies, family and gene studies, clinical trials, and human brain imaging research will be made clearer by revealing the pathophysiology of disorders that follow traumatic exposure. Analysis of postmortem tissue alone will not provide answers about functional neuronal circuitry but combining it with functional neuroimaging can answer many questions that neither type of study can alone. Once we have a working knowledge of the manner in which extreme environmental events affect the organism to alter central and peripheral neurobiology, we will be in an excellent position to develop secondary and tertiary prevention of acute and chronic posttraumatic pathological reactions. In addition, when we are able to identify genetic predictors for negative reactions to extreme environments, we will have made significant progress towards primary prevention.

The task of developing a collaborative project to obtain postmortem tissue is multifaceted. It involves efforts to establish a repository of post–mortem brain tissue from elderly subjects who had chronic PTSD as well as from young and middle- aged subjects who

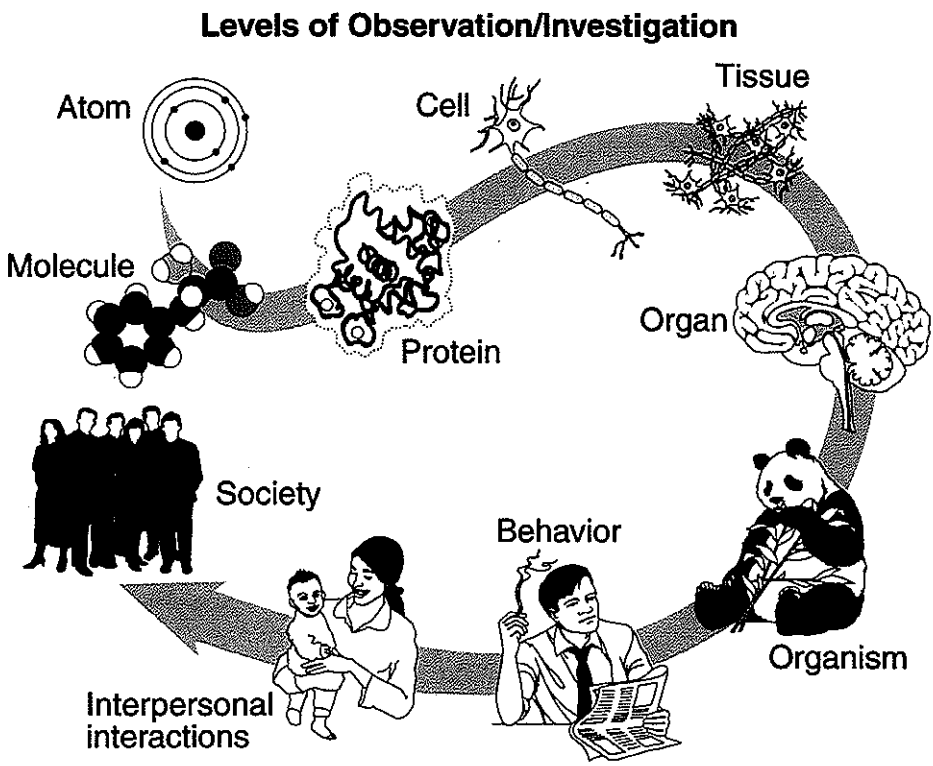

Figure 4.
Levels of observation/investigation beginning with the atom and ending with society: Scientists investigate the biological and/or psychological effects of environment-gene interactions at each of these levels.

had chronic PTSD. It involves collection of healthy controls, "resilient" people (those exposed to traumatic events who did not develop PTSD), and otherwise healthy subjects who experienced severe traumatic events in the days before an unexpected death (to look at the shorter term effects of traumatic exposure). Also needed are subjects with substance abuse and depression, to account for these frequently comorbid conditions.

Technical Challenges

The technical questions related to the development of a postmortem brain repository for severe traumatic exposure are important, and somewhat different from the challenges of other postmortem brain collections. Two primary areas for consideration are diagnosis and tissue processing.

Diagnosis. Traumatic experiences are difficult to assess posthumously as are posttraumatic symptoms. This is because people do not always talk about their traumatic life events with loved ones or family, and when they do they often do not describe their symptoms in specific detail. Issues related to subject recruitment raises several issues, including diagnosis and history of the subjects, presence of comorbid diagnoses, and peri–agonal events. These sorts of questions are not likely to be on the minds of next– of– kin after a death, and it may be unpleasant for family to recall such painful

times for the deceased. Obtaining information and agreement for donation of tissue from individuals before they die allows for more accurate assessment of life events and behavioral and subjective responses to those events. For example, identifying people who were prisoners– of– war, combat veterans, police officers, fire fighters or others known to be exposed to recurrent traumatic events, and asking them if they would like to participate in research that involves donating brain tissue after they die and completing assessments while alive, would provide greater diagnostic and symptom clarity.

Another challenge in recruitment involves the high prevalence of comorbid psychiatric diagnoses associated with exposure to severe trauma. For example, in addition to PTSD, many exposed individuals have depression (David et al., 1996; Green et al., 1992; McFarlane and Papay, 1992), substance abuse (Joseph et al., 1993; Pfefferbaum and Doughty, 2001; Sims and Sims, 1998; Smith et al., 1999; Vlahov et al., 2002), and other anxiety disorders (David et al., 1996; Green et al., 1992; McFarlane and Papay, 1992). Some people may develop depression and/or substance abuse following traumatic events but do not meet criteria for PTSD. Therefore, it will be necessary to have several groups of symptomatic, trauma–exposed subjects, each with particular diagnostic profiles. A related difficulty is recruiting subjects who are not exposed to traumatic events. Given the prevalence of natural disasters, interpersonal crime, automobile collisions, domestic abuse, and industrial accidents, it will be challenging to find control subjects who are not exposed to such events. And without direct communication with the individual while alive, it is challenging to know about exposure with accuracy.

Peri–agonal events that may affect brain tissue include use of medications or medical procedures (such as artificial ventilation) at and around the time of death. Method of death may also be a factor, since there are likely to be brain cell alterations following a slow, protracted illness compared with sudden death from, say, myocardial infarction. Such factors must be considered when tissue is evaluated for use in a postmortem tissue collection.

Tissue Processing. One of the factors in obtaining quality tissue is the time from the death of the subject to the preservation of the tissue on dry ice or by fixation, and the condition of the tissue before preservation. The time from death to preservation is called the "postmortem interval" and can make a profound difference in the quality of the sample for some observations (like measurement of neurotransmitters and enzymes) but not for others (like DNA, morphometric measures, etc.) (Everall and Harrison, 2002). The pH of the tissue and cerebral spinal fluid is important for determining the quality of the tissue, since pH is affected by the degree of hypoxia before death and related events that can degrade the quality of the tissue without regard to postmortem interval (Harrison et al., 1995). Other factors include mode of preservation of the tissue, method and thickness of tissue sectioning, and duration of storage. Before beginning a tissue collection, these factors need to be carefully considered with regard to the scientific questions one would like to answer. In addition, it is important for the control tissue and the experimental tissue to be processed in similar fashion.

The process of beginning and maintaining a postmortem brain tissue collection requires careful consideration of these and other factors if high quality, dependable material is to be made available for research.

CONCLUSIONS

The study of the interaction of genetic and environmental influence in psychiatric illness remains a challenging field of investigation. Recent expanding knowledge of PTSD, ASD, and animal studies of environmental effects on neurobiology have brought us to a new frontier of understanding of the brain–environment interaction. Our present knowledge would be greatly furthered by the

development of a brain tissue collection for the study of extreme environmental exposure. The known ways to approach uncovering the answer to brain–environment interactions involve studies of animals such as rodents and non–human primates, live humans (including families), and tissue from animals and humans. The limitations of our ability to alter human environments intentionally, and study the effects on brain and behavior directly, make certain experimental approaches in humans impossible.

The use of postmortem brain tissue from subjects with psychiatric conditions and healthy controls has led to advances in many areas of neuropsychiatry and promises to lead to more in the future. Advancing a brain collection specifically for the investigation of the effects of extreme environmental stressors fills a gap in the current research; it will provide another of the important pieces to the puzzle that constitutes the scientific investigation of both negative and positive effects of environmental exposures. In addition to facilitating new discoveries related to the psychiatric illnesses of ASD and PTSD, such a resource can enable scientists to correlate structural and functional imaging findings with tissue abnormalities, essential to validate the results of recent imaging studies.

Another important research question that waits to be addressed is the present problem of the confounding effects of environmental trauma on other neurological and psychiatric postmortem tissue studies. High rates of exposure to extreme environments are experienced by many populations. It will be important to understand the extent to which findings in postmortem studies of subjects with schizophrenia or bipolar disorder (or Alzheimer's Disease) may be influenced by traumatic exposure. While a difficult question, an answer may be found through the systematic study of the tissue from people who were exposed to extreme environmental stressors.

Thus, a center for postmortem tissue of people who have been exposed to traumatic events, and either had or did not have a negative result from that exposure, together with a non–exposed control group, is essential for facilitating research advances in understanding the etiology and pathophysiology of a number of psychiatric disorders, as well as resiliency or resistance to these disorders. Such a resource will facilitate the understanding of the role of the environment in all psychiatric conditions, the effects of exposure to traumatic events in other brain disorders already under study, and clarify the ways in which the environment influences genetic expression to produce behavioral alterations.

GLOSSARY

Adrenal medulla: n. The inner, reddish brown, soft part of the suprarenal gland (situated above the kidney); it synthesizes, stores, and releases catecholamines in response to environmental and physiological stress.

Adrenergic: adj. Liberating or activated by epinephrine or a substance like epinephrine.

Agonist: n. A substance that can interact with a receptor and initiate a physiological or pharmacological response characteristic of that receptor.

Alpha–receptors: n. These respond to epinephrine and norepinephrine release. They are located on the axon terminal, the cell body and the dendrites of nerve cells. They affect vascular dilatation, pupil contraction, and central nervous system processes.

Amygdala: n. One of the four basal ganglia in each cerebral hemisphere that is part of the limbic system and consists of an almond–shaped mass of gray matter in the roof of the lateral ventricle.

Antagonist: n. An agent that acts in physiological opposition; or a chemical that acts within the body to reduce the physiological activity of another chemical substance, especially one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its nervous receptor.

Apoptosis: n. Programmed cell death, the body's normal method of disposing of damaged, unwanted, or unneeded cells.

Asymptomatic: adj. Presenting no symptoms of disease.

Basolateral: adj. Basal (pertaining to or situated near a base) and lateral (pertaining to a side); specifically used to refer to one of the two major divisions of the amygdala.

Bcl–2: n. This gene product inhibits programmed cell death. A proto–oncogene, activated by chromosome translocation in human B–cell lymphomas. Encodes a plasma membrane protein.

Benzodiazepine: n. A chemical group that includes tranquilizers and any group of aromatic fat amines. These compounds bind to inhibitory receptors in the brain known as GABA receptors.

Beta–adrenergic receptors: n. A site in the autonomic nervous system in which adrenergic agents like norepinephrine and epinephrine are bound. They work by affecting the response to some nerve impulses in certain parts of the body. Activation of beta–receptors causes various physiological reactions, such as relaxation of the bronchial muscles and an increase in the rate and force of cardiac contraction.

Bipolar disorder: n. Any of several mood disorders characterized by alternating episodes of depression and mania or by episodes of depression alternating with mild or moderate nonpsychotic excitement—called also *bipolar affective disorder, bipolar illness* or *manic–depression.*

Candidate gene: n. A gene, located in a chromosome region suspected of being involved in a disease, whose protein product suggests that it could be the disease gene in question.

Catecholamine: n. Any of various substances (epinephrine, norepinephrine, and dopamine) that contain a benzene ring with two adjacent hydroxyl groups and a side chain of ethylamine and that function as hormones or neurotransmitters or both.

Complementary DNA (cDNA): n. A DNA that is complementary to a given RNA, which serves as a template for synthesis of the DNA in the presence of reverse transcriptase.

Cerebral cortex: n. The thin layer or mantle of gray substance covering the surface of each cerebral hemisphere, responsible for higher mental functions, general movement, perception, behavioral reactions, and the association and integration of these functions. It has been divided into functional areas such as motor areas, primary or receiving areas, and association areas. It has also been divided into six cell layers or layers of variable numbers and arrangements of cell fiber layers.

Chromosome: n. One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mothers and half from their fathers.

Chromosome translocation: n. A chromosomal segment transferred to a new position.

Corticosteriod n. Any of various adrenal–cortex steroids (such as corticosterone, cortisone, and aldosterone) used especially as anti–inflammatory agents.

Cytoarchitecture: n. The cellular makeup of a bodily tissue or structure.

Diencephalon: n. The posterior subdivision of the forebrain, also called interbrain or between brain.

Dopamine: n. 1: A monoamine neurotransmitter formed in the brain by the decarboxylation of dopa. It is essential to the normal functioning of the central nervous system. A reduction in its concentration within the brain is associated with Parkinson's disease. 2: A monoamine C8H11NO2 that is a decarboxylated form of dopa and occurs especially as a neurotransmitter in the brain and as an intermediate in the biosynthesis of epinephrine.

Dysphoria: n. A state of feeling unwell or unhappy.

Epidemiology: n. A branch of medical science that deals with the incidence, distribution and control of disease in a population.

Epinephrine: n. A colorless, crystalline, weakly basic sympathomimetic (viz., stimulating the sympathetic nervous system) hormone that is the principal blood–pressure–raising hormone selected by the adrenal medulla. It is prepared from adrenal extracts or made synthetically, and is used medicinally especially as a heart stimulant, as a vasoconstrictor in controlling hemorrhages of the skin, in prolonging the effects of local anesthetics, and as a muscle relaxant in bronchial asthma.

Excitotoxicity: n. The process by which an agent binds to a nerve cell receptor, stimulates the cells excessively, and thereby damages it or causes its death.

Functional MRI (fMRI): n. Functional Magnetic Resonance Imaging (fMRI) is a technique for determining which parts of the brain are activated by different types of physical sensation or activity, such as sight, sound or the movement of a subject's fingers. This "brain mapping" is achieved by setting up an advanced MRI scanner in a special way so that the increased blood flow to the activated areas of the brain shows up on Functional MRI scans. It also aims to determine the neurobiological correlate of behavior by identifying the brain regions that become more "active" during the performance of specific cognitive and emotional tasks.

Gene therapy: n. The insertion of usually genetically altered genes into cells especially to replace defective genes in the treatment of genetic disorders or to provide a specialized disease–fighting function (such as the destruction of tumor cells).

Glial: adj. Of or relating to glia (the supportive cells in the central nervous system—the brain and spinal cord).

Glucocorticoid: n. Any group of corticosteroids produced by the adrenal cortex (outer, firm, yellowish layer of the adrenal gland) that regulate carbohydrate, protein, and fat metabolism that tend to increase liver glycogen and blood sugar by increasing gluconeogesis. They also affect the muscle tone and microcirculation, participate in the maintenance of blood pressure, increase gastric secretion, alter connective tissue response to injury, impede cartilage production, and inhibit inflammatory, allergic and immunological responses. Glucocorticoids are produced normally by the adrenal cortex and provide for the response to stress.

Gluconeogesis: n. The formation of glucose from molecules that are not themselves carbohydrates, such as amino acids, lactate and the glycerol portion of fats.

Glycogen: n. A tasteless polysaccharide composed of glucose molecules constituting the principle form in which carbohydrate energy is stored in animals. It is stored in the liver but also present in muscles, and readily broken down to be used as an energy source in metabolic pathways. Also called animal starch.

Glycogen synthase kinase–3: n. A protein kinase involved in tumorigenesis, differentiation and apoptosis.

Grey matter: n. Neural tissue especially of the brain and spinal cord that contains cell bodies as well as dendritic fibers, has a brownish gray color, and forms most of the cortex and nuclei of the brain, the columns of the spinal cord, and the ganglia.

Guanosine trisphosphate: n. A nucleotide, the 5'–triphosphate of guanosine, it is an activated precursor in the synthesis of ribonucleic acid and is also involved in energy metabolism, being produced from guanosine 5–diphosphate by substrate level phosphorylation in the tricarboxylic acid cycle and serving as a source of free energy to drive protein synthesis.

Hippocampus: n. In the brain, a curved elongated ridge that is an important part of the limbic system, extends over the floor of the descending horn of each lateral ventricle of the brain, and consists of grey matter covered on the ventricular surface with white matter. It is involved in the complex processes of forming, sorting, and storing memories. It can combine and store temporal, spatial and sensory cues into representations that are stored immediately. It can also filter and combine information from one or several sensory streams into

elements that allows associations to be created.

Histopathology: n. A branch of pathology concerned with the tissue changes characteristic of disease.

Huntington's disease: n. A degenerative brain disorder that usually appears in mid life. The genetic defect responsible is a small sequence of DNA on chromosome 4 in which several base pairs are repeated many times. Its symptoms, which include involuntary movement of the face and limbs (chorea), mood swings, and forgetfulness, get worse as the disease progresses. It is generally fatal within 20 years.

Hypothalamus: n. A basal part of the diencephalon that lies beneath the thalamus on each side, forms the floor of the third ventricle, and includes vital autonomic regulatory centers (as for the control of food intake, water balance, temperature, and sleep).

Hypothalamic–Pituitary–Adrenal axis (HPA axis): n. The HPA axis is the classical neuroendocrine system that responds to stress and whose final product, corticosteroids, targets components of the limbic system, particularly the hippocampus.

Hypoxia: n. A deficiency of oxygen reaching the tissues of the body.

Inositol: n. Any of several crystalline stereoisomeric cyclic alcohols $C_6H_{12}O_6$.

Isoproterenol: n. A drug used to prevent and treat wheezing, shortness of breath and troubled breathing caused by asthma, chronic bronchitis, emphysema and other lung diseases. It relaxes and opens air passages in the lungs, making it easier to breathe. It is structurally related to epinephrine but acts exclusively on beta–receptors.

Knockout: n., adj. Inactivation of specific genes. Knockouts are often created in laboratory organisms such as yeast or mice so that scientists can study the knockout organism as a model for a particular disease.

Limbic system: n. A term loosely applied to a group of brain structures common to all mammals, associated with olfaction (smell) but of greater importance in other activities such as autonomic functions, and certain aspects of emotion and behavior.

Locus coeruleus: n. A blue area of the brain stem with many norepinephrine–containing neurons. The function of the locus coeruleus is to determine whether attention is being focused on the external environment, prioritize competing incoming stimuli, and determine where attention will be fixed. It also has influence in cognition, mood, emotions, movement and blood pressure.

Messenger RNA (mRNA): n. Template for protein synthesis. Each set of three bases, called a codon, specifies a certain amino acid, which then bonds to other amino acids to make up a protein. The sequence of a strand of mRNA is based on the sequence of a complementary strand of DNA.

Morphometry: n. The quantitative measurement of the form, especially of living systems or their parts.

Neuroglia: n. The supporting structure of nervous tissue.

Neuropeptide: n. An endogenous (developing or originating within the organism) peptide (any member of a class of low molecular weight compounds that include two or more amino acids) that influence neural activity or functioning (as an endorphin or an enkephalin).

Neuropeptide Y: n. A substance that sometimes functions as a neurotransmitter. Some research shows that neuropeptide Y may be involved with Alzheimer's disease.

Neurotransmitter: n. A substance (such as norepinephrine or acetylcholine) that transmits nerve impulses across a synapse.

Norepinephrine: n. A catecholamine that is transmitted across neuronal synapses to the postganglionic neurons of the sympathetic nervous system. Closely related to the compound epinephrine that is released by the adrenal medulla. Its major effects include increasing heart rate, blood pressure and cardiac output, constricting blood vessels, increasing glycogenolysis and lypolysis (to mobilize energy), and relaxation of respiratory bronchial smooth muscle. In general, it prepares the body for "fight or flight" during times of acute stress.

Nucleotide: n. Any of several compounds that consist of a ribose or deoxyribose sugar joined to a purine or pyrimidine base and to a phosphate group and that are the basic structural units of RNA and DNA.

Oncogene: n. A gene that is capable of causing

the transformation of normal cells into cancer cells.

Pathophysiology: n. Derangement of function seen in disease; alteration in function as distinguished from structural defects.

Positron–emission tomography (PET): n. An imaging modality in which in vivo, noninvasive, cross–sectional images of a body area of interest are obtained. It involves the use of gamma radiation given off in the collision of electrons in cells with positrons emitted by radionuclides incorporated into metabolic substances, such as water or glucose.

Positron: n. Positively charged particle having the same mass and magnitude of charge as the electron and constituting the anti–particle of the electron—also called *positive electron.*

Propranolol: n. A beta–blocker used in the form of its hydrochloride in the treatment of abnormal heart rhythms, angina pectoris, and hypertension.

Radionuclide: n. A radioactive nuclide (an atom characterized by the content of its nucleus and hence the number of protons, electrons, and neutrons).

Radioligand: n. A substance (as an antigen) that has been radiolabeled especially for analysis by radioimmunoassay.

Sensorimotor cortex: n. Both sensory and motor, as parts of the cerebral cortex, of or pertaining to motor activity caused by sensory stimuli.

Serotonergic: adj. Liberating, activated by, or involving serotonin in the transmission of nerve impulses.

Serotonin: n. Found in various animals, bacteria and plants. In humans, it is synthesized in the intestinal chromaffin cells and in the central and peripheral neurons and is found in high concentration in many body tissues, including the intestinal mucosa, pineal body and the central nervous system. It inhibits gastric secretion, stimulates smooth muscles, serves as a central neurotransmitter, and is a precursor of melatonin. It is also called 5–hydroxytryptamine or 5–HT.

Single photon emission computed tomography (SPECT): n. A medical imaging technique that is used especially for mapping brain function and that is similar to positron–emission tomography in using the photons emitted by the agency of a radioactive tracer to create an image but that differs in being able to detect only a single photon for each nuclear disintegration and, therefore, generates a lower–quality image.

Synaptic plasticity phenomena: n. Believed to be the physiological basis of learning, memory and some aspects of development. It is generally believed that information can be stored in the brain as changes in the efficacy of synapses between input and output neuronal pathways. That is, after conditioning stimulation, synaptic responses are increased or decreased, and such synaptic plasticity can persist for an extended period of time. Thus, synaptic plasticity is a likely candidate for the cellular mechanisms that underlie learning and memory in the mammalian brain.

Tumorigenesis: n. The production of tumors.

Tyrosine kinase receptor: n. Any group of enzyme–linked receptors of the transferase class that catalyze the phosphorylation of tyrosine residues in specific membrane vesicle associated proteins. The enzyme activity is present in certain membrane proteins and is a product of some oncogenes.

Vasopressor: n. Any substance that stimulates contraction of the muscular tissue of the capillaries and arteries.

Ventral endopiriform nucleus: n. A large group of multi–polar cells located deep to the piriform cortex of the brain. The function of this nucleus is unknown, but studies with animal models suggest that it plays an important role in temporal lobe epilepsy.

White matter: n. Nerve cell tissue composed of myelin–coated fiber tracts. White matter carries information between nerve cells in the brain and through the spinal cord. The inner portion of the cerebral hemispheres is composed of white matter.

Yohimbine: n. An indole alkaloid, extracted from the bark of Corynanathe johimbe or Rauwolfia serpentina; an alpha–2 adrenergic antagonist (viz., a compound that opposes the physiological effects of alpha–2 adrenergic compounds at the receptor level); purported to have aphrodisiac properties, it has limited clinical usefulness.

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